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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,574	07/20/2001	Frank A. Skraly	MBX 039	2982

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EXAMINER	
PAK, YONG D	
ART UNIT	**PAPER NUMBER**
1652	

MAIL DATE	DELIVERY MODE
07/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/909,574	**Applicant(s)** SKRALY ET AL.	
	Examiner Yong D. Pak	**Art Unit** 1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 22 June 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *02 June 2007*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-4 and 6-10*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

ADVISORY ACTION

Response to Arguments

The amendment filed on June 22, 2007 under 37 CFR 1.116 in reply to the final rejection has been considered and has been entered but is not deemed to place the application in condition for allowance because: the amendment and request for consideration does not overcome the rejection of claims 1-4 and 6-10 under 35 U.S.C. 103(a) as being unpatentable over Skraly, Madison et al., and BRENDA database, as discussed below.

Claims 1-4 and 6-10 are pending.

Response to Arguments

Applicant's arguments filed June 22, 2007 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

Claims 1-4 and 6-10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Skraly, Madison et al., and BRENDA database.

Claims 1-4 and 6-10 are drawn to a method of producing PHAs by providing an *E. coli*, which expresses acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase or PHA synthase, wherein said bacteria is genetically

engineered to express polynucleotides that encode a diol oxidoreductase or aldehyde dehydrogenase, wherein the enzyme expressed by the bacteria convert 1,6-hexandediol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethanediol or 1,2-propanediol into 6-hydroxyhexanoate, 5-hydroxyvalerate, 4-hydroxybutyrate, 2-hydroxyethanoate or 2-hydroxypropionate monomers, respectively, and producing PHAs having a weigh-average molecular weight of at least 300,000 Da.

Skraly (*Polyhydroxyalkanoates Produced by Recombinant E. coli*, Poster at Engineering Foundation Conference: Metabolic Engineering, 1998 – cited previously on form PTO-892) discloses a method of producing PHA from 1,3-propanediol using recombinant *E. coli* expressing PHA synthase and diol oxidoreductase (pages 8-9), wherein said diol is oxidized to its corresponding aldehyde and then converted to its corresponding hydroxyalkanoate monomer via an aldehyde dehydrogenase and CoA transferase (page 8). *E. coli* produces aldehyde dehydrogenase naturally (see "aldehyde dehydrogenase" – cited previously on form PTO-892). Skraly also discloses (1) PHA monomers other than 3-hydroxybutyrate that can improve flexibility and reduce crystalline of the resulting PHA polymer, such as 5-hydroxyvalerate and 4-hydroxybutyrate (page 6) and (2) new inexpensive starting materials for PHA synthesis, such as diols, 1,3-propanediol, 1,5-pentanediol, 1,4-butanediol and 1,2-propanediol, which are converted into their respective PHA monomers, 3-hydroxybutyrate, 5-hyroxyvalerate, 4-hydroxybutyrate and 2-hydroxypropionate (pages 1, 6 and page 8).

The difference between the reference of Skraly and the instant invention is that the reference of Skraly teaches does not teach a method of producing PHA from 1,6-

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[Date of extinction of right]

hexanediol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethandiol and 1,2-propanediol using an *E. coli* expressing diol oxidoreductase and acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase or PHA synthase.

Madison et al. (Metabolic engineering of poly(3-hydroxyalkanoates): from DNA to plastic. Microbiol Mol Biol Rev. 1999 Mar;63(1):21-53 – form PTO-1449) is cited here to provide evidence to support the level of skill in the art of recombinant organism expressing all genes necessary to produce PHAs. Madison et al. also teaches that the molecular mass of PHAs produced varies from 50,000 to 1,000,000 Da and bacterially produced PHAs have a high molecular mass (page 22). As applicants have stated, "one of skill in the art was capable of making and using genetically engineered plants for production of PHAs... all the genes necessary to implement the production of PHAs from feedstock such as diols have been cloned and are available in genetically manipulatable form, any combination of plasmid-borne and integrated genes may be used in the production of PHAs in organism such as plants.. it is routine in the art to incorporate the gene into a plasmid for expression in cells" (Appeal Brief, pages 24-25).

BRENDA database ("EC 1.1.1.202"– form PTO-892) discloses several diol reductases that oxidize diols and that have been cloned and expressed in *E. coli,* including the *K. pneumoniae* diol oxidoreductase used by Skraly and in the instant invention. Further, BRENDA database discloses a 1,3-propanediol dehydrogenase isolated from C. *freundii* which oxidizes several diols, 1,3-propanediol, 1,2-propanediol and 1,4-butanediol, and its expression in *E. coli* (pages 2-3). This enzyme has been cloned and expressed in *E. coli* (pages 10 and 12) as evidenced by Daniel et al. (J

Bacteriol. 1995 Apr;177(8):2151-6 - form PTO-892). Daniel et al. also teaches that said enzyme oxidizes all primary, secondary and tertiary alcohols (Daniel et al. on page 5152). Even though 1,5-pentanediol, 1,6-hexanediol and 1,2-ethanediol are not explicitly listed as one of the substrates, since the enzyme is able to oxidize primary alcohols and diols containing two primary alcohols, one having ordinary skill in the art would have reasonably expect the enzymes to oxidize 1,5-pentanediol, 1,6-hexanediol and 1,2-ethanediol. Also, one having ordinary skill in the art would have used other diol reductases of BRENDA database to oxidize the recited diols.

Therefore, combining the teachings of the above references, it would have been obvious to one having ordinary skill in the art to use the method of Skraly et al. in making PHAs by using other diols, such as 1,6-hexandediol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethanediol or 1,2-propanediol, by converting said diols into their respective PHA monomers using a recombinant *E. coli* that expresses acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase or PHA synthase as taught by Madison et al, and that also expresses a diol oxidoreductase. One of ordinary skill in the art would have been motivated to produce PHA from the recited diols in order to produce novel PHAs using inexpensive starting materials. One of ordinary skill in the art would have had a reasonable expectation of success since Skraly teaches a method of producing PHAs from a diol using a diol oxidoreductase/aldehyde dehydrogenase, Madison et al. teaches expression of genes necessary for PHA synthesis and BRENDA database teaches several diol oxidoreductases that have been cloned into *E. coli* that have a wide range in substrate

specificity. One having ordinary skill in the art would have had a reasonable expectation of success since production of PHAs in recombinant organism, such as *E. coli*, expressing enzymes necessary for PHA production is well known in the art and diol oxidoreductases, which have been cloned and expressed in *E. coli*, having a wide range of substrate specificity are well known in the art.

Therefore, the above references render claims 1-4 and 6-10 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the claims are not obvious over the cited references because Skraly does not disclose a method that can convert diols into 6-hydroxyhexanoate (1,6-hexanediol), 5-hydroxyvalerate (1,5-pentanediol), 4-hydroxybutyrate (1,4-butanediol), 2-hydroxyehtanote (1,2-ethanediol) and 2-hydroxypropionate (1,2-propanediol). Examiner respectfully disagrees. Skraly discloses new routes for producing PHAs, such as 1,2-propanediol (converted to 2-hydroxypropionate), 1,4-butanediol (converted to 4-hydroxybutyrate) and 1,5-butanediol (converted to 5-hydroxyvalerate) (pages 1, 6-7 and 9). Since Skraly discloses new monomers/starting materials and routes for PHA synthesis of Skraly, it would have been obvious to one having ordinary skill in the art to generate PHAs comprising of 5-hydroxyvalerate, 4-hydroxybutyrate or 2-hydroxypropionate from 1,5-pentanediol, 1,4-butanediol or 1,2-propanediol, respectively, or convert other structurally similar diols,

such as 1,6-hexanediol into 6-hydroxyhexanoate and 1,2-ethanediol into 2-hydroxyethanoate by using *E. coli* expressing diol oxidoreductase available in the art.

Applicants also argue since one skilled in the art must be provided with both a substrate and enzyme to make a desired product and since it is not an inherent outcome that merely because an organism has been shown to produce the desired product, or has been provided with an appropriate substrate, or even that an organism expresses one or more of the required enzymes, that one will produce the desired product, the claims are not obvious. Examiner respectfully disagrees. Obviousness does not require absolute predictability.

Applicants also argue that Madison et al. and Brenda database do not teach converting diols into PHA monomers. The rejection is based on the combined teachings of Skraly, Madison and BRENDA. The reference of Madison is used for its disclosure of supporting the level of skill in the art of recombinant organism expressing all genes necessary to produce PHAs and the reference of Brenda database is used for its teaching of many diol oxidoreductases available to one having ordinary skill in the art. Skraly et al. provides teachings of converting diols into PHA monomers.

Applicants also argue use of improper hindsight reasoning. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only

from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, it should be noted that as applicants have stated, "one of skill in the art was capable of making and using genetically engineered plants for production of PHAs... all the genes necessary to implement the production of PHAs from feedstock such as diols have been cloned and are available in genetically manipulatable form, any combination of plasmid-borne and integrated genes may be used in the production of PHAs in organism such as plants.. it is routine in the art to incorporate the gene into a plasmid for expression in cells" (Appeal Brief, pages 24-25). Madison et al. provides evidence to support the level of skill in the art of recombinant organism expressing all genes necessary to produce PHAs. Also, since knowledge of making PHA from a diol, 1,3-propanediol, using a recombinant *E. coli* expressing a diol oxidoreductase and genes necessary in PHA synthesis was well known, a method of making PHA from other diols was well within the level of one having ordinary skill in the art at the time the invention was made.

Hence the rejection is maintained.

Conclusion

None of the claims are allowable

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935.

The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Yong D. Pak
Patent Examiner 1652